Amino Acids (2019) 51:977–982
https://doi.org/10.1007/s00726-019-02738-x

SHORT COMMUNICATION

Distinct associations between plasma osteoprotegerin, homoarginine and asymmetric dimethylarginine in chronic kidney disease male patients with coronary artery disease

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Received: 28 March 2019 / Accepted: 25 April 2019 / Published online: 2 May 2019
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Abstract

High plasma osteoprotegerin (OPG) and asymmetric dimethylarginine (ADMA) and low homoarginine (hArg) predict adverse renal and cardiovascular (CV) outcomes. In patients with chronic kidney disease and stable coronary artery disease, plasma OPG correlated with hArg ($r = -0.37$, $P = 0.03$) and the hArg/ADMA molar ratio ($r = -0.46$, $P = 0.009$), which was maintained upon adjustment for renal function. Elevated OPG levels and decreased hArg/ADMA ratios independently predicted 4-year composite CV and renal endpoints (CV death or progression to dialysis). Thus, high OPG and low hArg/ADMA ratio, albeit interrelated, appear to independently contribute to adverse clinical outcome.

Keywords ADMA · CAD · CKD · Homoarginine · Kidney · Osteoprotegerin

Abbreviations

ADMA	Asymmetric dimethylarginine
AGAT	L-Arginine:glycine amidinotransferase
CAD	Coronary artery disease
CKD	Chronic kidney disease
CV	Cardiovascular
ΔeGFR	eGFR change
eGFR	Estimated glomerular filtration rate
hArg	L-Homoarginine
NO	Nitric oxide
NOS	Nitric oxide synthase
OPG	Osteoprotegerin

Handling Editor: E. Closs.

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Introduction

Osteoprotegerin (OPG) is expressed by osteoblasts, cytokine-activated endothelia, vascular myocytes and macrophages and predicts adverse cardiovascular (CV) outcome in the general population (Kiechl et al. 2004; Semb et al. 2009; Lieb et al. 2010; Tschiderer et al. 2017) and in various clinical settings (Tschiderer et al. 2018), including patients with chronic kidney disease (CKD) (Mesquita et al. 2009; Lewis et al. 2015; Kuźniewski et al. 2016; Yilmaz et al. 2016), stable coronary artery disease (CAD) (Bjerre et al. 2014) and acute coronary syndromes (Røysland et al. 2012). Elevated OPG levels are also associated with future rapid renal function decline in elderly women (Lewis et al. 2014) and progression to end-stage renal-disease in type 1 diabetes mellitus (Jorsal et al. 2008). OPG affects numerous intracellular pathways that modulate activation and propensity to apoptosis (Venuraju et al. 2010).

In subjects with CAD (Morisawa et al. 2015) and essential hypertension (Tsioufis et al. 2011), OPG correlated positively with asymmetric dimethylarginine (ADMA), a recognized predictor of CV risk (Böger et al. 2009) and CKD progression (Fliser et al. 2005; Ravani et al. 2005).

ADMA originates from the proteolysis of proteins methylated on Arg residues by protein arginine methyltransferase 1 (PRMT1; EC 2.1.1.125). hArg is primarily of renal origin and is biosynthesized by L-arginine:glycine amidinotransferase (AGAT; EC 2.1.4.1). To the best of our knowledge, no studies have dealt with relations of OPG and L-homoarginine (hArg), an emerging risk factor in the renal and CV systems (März et al. 2010; Atzler et al. 2013, 2014; Choe et al. 2013; Drechsler et al. 2013; Kleber et al. 2013; Ravani et al. 2013; Pilz et al. 2014; Frenay et al. 2015; Kayacelebi et al. 2017; Zinellu et al. 2018).

Associations of CV mortality risk with high OPG (Lewis et al. 2015) or low hArg (Tomaschitz et al. 2014) concentrations are considerably stronger in subjects with an estimated GFR (eGFR) below 60 mL/min/1.73 m^2. We, therefore, hypothesized that the kidneys may play a major role both in the homeostasis and modulation of biological effects of hArg and OPG in CKD patients with CAD. The primary aim of the present study was to test for mutual associations between OPG, hArg and ADMA in plasma of patients with CKD and CAD. We also tested a potential prognostic value of OPG with regard to 1-year renal function decline and 4-year clinical outcome in patients with both CAD and predialysis CKD.

Methods

Patients

Forty men with CKD were recruited from non-smoking patients admitted to the Second Department of Cardiology of Jagiellonian University Medical College for elective coronary angiography for stable CAD (Table 1). All CKD subjects were free of heart failure, left ventricular systolic dysfunction (ejection fraction ≥ 50% by echocardiography), clinical instability or coexistent diseases except for well-controlled type 2 diabetes mellitus or hypertension. Patients

Table 1 Patients' characteristics and plasma concentrations of biochemical parameters according to 1-year GFR change (ΔeGFR) and 4-year composite clinical outcome

Characteristic	1-year eGFR changes (ΔeGFR)		*P*	Progression to dialysis or death within 4 years		*P*
	< Median	> Median		Progressors	Non-progressors	
Age (years)	67 ± 11	59 ± 17	NS	67 ± 10	60 ± 16	NS
Hypertension *n* (%)	19 (95%)	17 (85%)	NS	12 (80%)	24 (96%)	NS
Diabetes *n* (%)	7 (21%)	7 (21%)	NS	5 (33%)	9 (36%)	NS
eGFR (mL/min/1.73 m^2)	29 ± 19	37 ± 28	NS	25 ± 18	38 ± 24	0.08
ΔeGFR (mL/min/1.73 m^2)	− 4.3 ± 2.5	8.7 ± 11.4	**< 0.001**[a]	− 1.8 ± 5.3	5.2 ± 11.9	**0.04**[a]
BMI (kg/m^2)	28.7 ± 3.8	27.7 ± 3.6	NS	28.1 ± 2.7	28.4 ± 3.9	NS
Hemoglobin (g/dL)	12.0 ± 2.1	13.4 ± 1.8	NS	11.7 ± 2.0	13.2 ± 1.9	NS
LDL-cholesterol (mM)	2.2 ± 0.7	2.4 ± 0.8	NS	2.3 ± 0.7	2.4 ± 0.6	NS
HDL-cholesterol (mM)	1.2 ± 0.3	1.3 ± 0.3	NS	1.2 ± 0.2	1.4 ± 0.3	NS
Triglycerides (mM)	1.5 ± 0.5	1.7 ± 0.5	NS	1.6 ± 0.6	1.6 ± 0.5	NS
hs-CRP (mg)/L	3.8 [1.6–5.9]	2.9 [0.9–5.4]	NS	4.5 [1.6–5.4]	2.9 [0.9–5.1]	NS
Calcium (mM)	2.2 ± 0.2	2.4 ± 0.2	NS	2.2 ± 0.3	2.3 ± 0.1	NS
Phosphate (mM)	1.1 ± 0.2	1.2 ± 0.2	NS	1.2 ± 0.2	1.1 ± 0.2	NS
Osteoprotegerin (μg/L)	2.7 [2.5–3.0]	2.1 [1.6–3.5]	0.07	3.0 [2.5–3.9]	1.9 [1.6–2.7]	**0.002**[a]
Arg (μM)	245 [178–408]	294 [274–396]	NS	352 [260–521]	278 [210–299]	0.06
ADMA (μM)	0.63 [0.58–0.75]	0.60 [0.54–0.74]	NS	0.73 [0.61–0.78]	0.60 [0.55–0.64]	0.08
Arg/ADMA ratio	388 [262–626]	517 [424–655]	NS	468 [293–706]	448 [337–609]	NS
hArg (μM)	0.99 [0.67–1.46]	1.19 [0.62–2.05]	NS	0.97 [0.67–1.29]	1.34 [0.60–1.93]	NS
Arg/hArg ratio	261 [144–429]	280 [150–483]	NS	344 [248–595]	204 [121–422]	0.06
hArg/ADMA ratio	1.82 [1.19–2.28]	1.60 [1.17–3.30]	NS	1.31 [1.09–1.76]	2.28 [1.30–3.15]	**0.025**[a]
Nitrite (μM)	2.47 [2.12–2.86]	2.40 [2.12–2.74]	NS	2.52 [2.20–2.76]	2.40 [2.07–2.98]	NS
Nitrate (μM)	83 [58–119]	87 [66–115]	NS	72 [57–108]	87 [68–118]	NS
MDA (μM)	1.40 [0.96–1.59]	0.93 [0.74–1.39]	NS	1.11 [0.92–3.01]	1.05 [0.70–1.58]	NS

Data are shown as mean ± SD or median [interquartile range]

hs-CRP high-sensitive C reactive protein, *MDA* malondialdehyde

[a]Statistically significant intergroup differences are marked in bold

with relevant abnormalities in routine blood assays or with prehospital evidence of unstable creatinine levels were excluded. All patients were on a standard medical therapy recommended by practice guidelines, including low-dose aspirin, statins and angiotensin-converting enzyme inhibitors for at least 3 months prior to the index hospitalization. CKD diagnosis was based on an eGFR value between 15 and 59 mL/min/1.73 m^2 by the CKD-EPI formula, corresponding to eGFR stages G3–G4 according to 2011 KDIGO classification of CKD (Levey et al. 2011).

Follow-up data were collected during routine control visits in our outpatient clinic, including control creatinine assay performed 12 ± 1 months after discharge. Patients or their relatives were contacted by telephone for the occurrence of a 4-year composite adverse clinical outcome, i.e., combined progression to dialysis or death from a CV cause, which was then confirmed by the review of medical records.

The study was approved by the Bioethics Committee of the Jagiellonian University (ethical approval No. KBET/364/B/2012) in adherence to the Declaration of Helsinki. All participants provided written informed consent.

Biochemical analyses

OPG, hArg, ADMA and other biomarkers were measured in available EDTA plasma samples ($n = 36$, 35 and 32 for OPG, hArg and ADMA, respectively). OPG was measured by an enzyme immunoassay (R&D Systems, Minneapolis, MN, USA). LDL and HDL cholesterol, triglycerides, hemoglobin, creatinine and high-sensitive C-reactive protein (hs-CRP) were determined by standard clinical chemistry laboratory assays. Amino acids, malondialdehyde (MDA), nitrite and nitrate were analyzed by fully validated gas chromatography-mass spectrometry (GC–MS) methods as described previously (Tsikas 2017; Hanff et al. 2017, 2019).

Statistical analysis

Data are presented as mean ± SD, median [interquartile range: 25th–75th percentile] or numbers and percentages. Normality was evaluated by Shapiro–Wilk's test. Patients' characteristics were compared according to the 1-year eGFR change (ΔeGFR), dichotomized with the reference to the median value of −0.9 mL/min/1.73 m^2, or to a 4-year progression to dialysis or CV death. Intergroup differences in continuous data were estimated by two-tailed Student's t test (or Welch's t test in case of inhomogeneous variances assessed by Levene's test) with prior decadic logarithmic ($\log_{10}$) transformation; proportions were compared by Chi-squared test. Bivariate Pearson's correlation coefficients (r_P) were calculated. Multiple logistic regression was used to estimate mutual independence of prognosticators with regard to the prediction of the progression to dialysis or the occurrence of CV death during a 4-year follow-up. Two-tailed P values < 0.05 were considered statistically significant.

Results

The concentrations of the biomarkers measured in the plasma samples of the study's patients are summarized in Table 1. The relationships between OPG, hArg and ADMA are illustrated in Fig. 1.

Baseline plasma cocentrations of hArg and OPG correlated negatively with each other ($r_P = -0.371$, $P = 0.03$; Fig. 1a), which was maintained upon adjustment for eGFR. In contrast, baseline ADMA and OPG levels were positively correlated ($r_P = 0.385$, $P = 0.03$; Fig. 1b). The hArg/ADMA molar ratio correlated inversely with plasma OPG ($r_P = -0.46$, $P = 0.009$; Fig. 1c). ADMA and hArg concentrations were unrelated ($r_P = -0.243$, $P = 0.187$).

Six patients progressed to dialysis and nine died from CV causes over the subsequent 4 years. In these 15 patients (progressors), plasma OPG concentration was higher (3.0 [2.5–3.9] vs. 1.9 [1.6–2.7] µg/L, $P = 0.002$) and the hArg/ADMA molar ratio was lower (1.31 [1.09–1.76] vs. 2.28 [1.30–3.15], $P = 0.025$) compared to the remainder (non-progressors) (Table 1). Neither hArg nor ADMA plasma concentrations differed statistically significantly between progressors and non-progressors (Table 1). One-year eGFR decline was more pronounced in patients who developed future CV or renal endpoints ($P = 0.04$) (Table 1).

Multiple logistic regression revealed that higher OPG concentrations and lower hArg/ADMA ratios independently predicted 4-year composite CV and renal endpoints. Mean adjusted odds ratio for the adverse outcome was 1.30 [95% confidence interval, 1.03–1.64] ($P = 0.02$) per 1-µg/L increment in OPG and 0.3 [0.1–0.9] ($P = 0.03$) per 1-unit increase in the hArg/ADMA molar ratio (Hosmer–Lemeshow goodness-of-fit test, $P = 0.3$).

Discussion

To the best of our knowledge, a relationship between hArg and OPG has not been reported so far. Thus, our small study supplements previous observations of a positive correlation of OPG and ADMA in CAD (Morisawa et al. 2015) and essential hypertension (Tsioufis et al. 2011).

The patients' plasma OPG concentrations were within reported ranges (Bjerre et al. 2014; Lewis et al. 2014), hArg levels were lower compared to healthy men or women (Kayacelebi et al. 2014a, b; Atzler et al. 2016), while ADMA was higher than in CAD patients (Thum et al. 2005). The hArg/ADMA molar ratio was lower in our

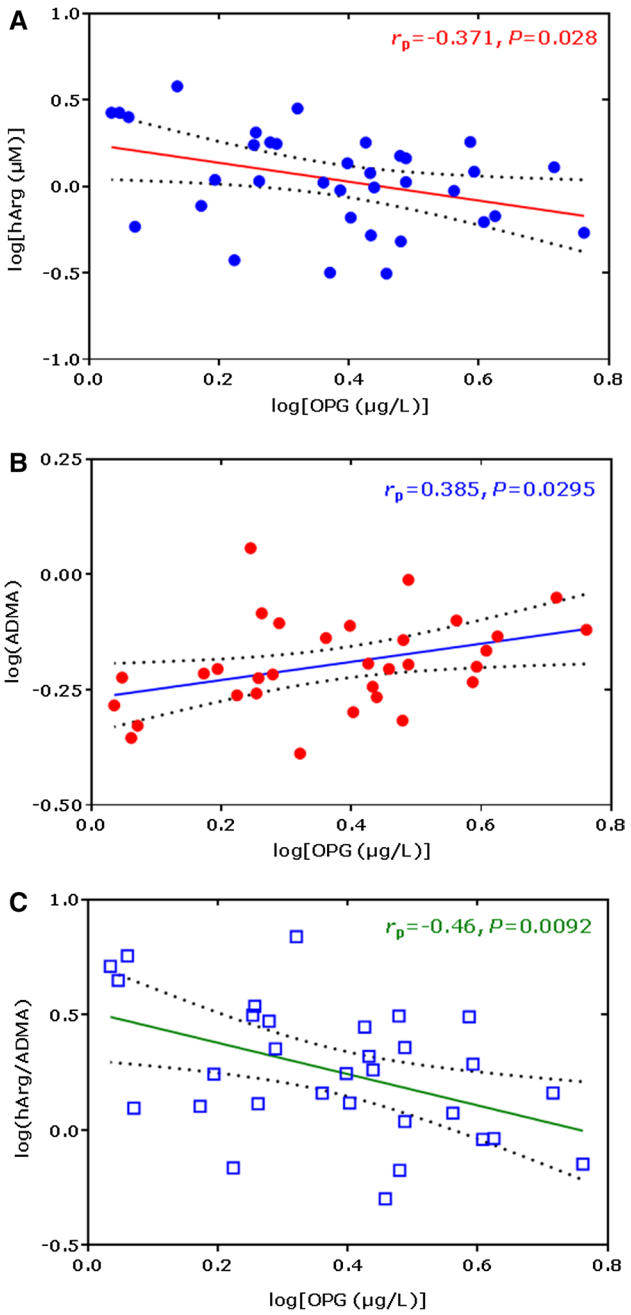

Fig. 1 Relationships between the plasma concentrations of OPG, hArg and ADMA in the study's patients at baseline. Pearson's correlation coefficients (r_P) between OPG and hArg (**a**), OPG and ADMA (**b**), and OPG and the hArg/ADMA molar ratio (**c**)

study group versus healthy subjects (Tsikas and Kayacelebi 2014). Plasma nitric oxide (NO) metabolites nitrite and nitrate and the lipid peroxidation biomarker MDA were within references ranges reported previously (Hanff et al. 2017; Tsikas 2017). As ADMA and hArg are formed from Arg in distinctly different pathways involving PRMT1 and AGAT, respectively, our observations suggest diminished AGAT activity, elevated PRMT1 activity, unaltered NOS activity and lipid peroxidation in our patients.

Given that elevated OPG, higher ADMA and lower hArg are established risk factors for renal and CV morbidity and mortality, it may suggest their synergistic contribution to the risk in patients with CKD and coexistent CAD via different detrimental pathways in the kidney and the vasculature. That high OPG and low hArg/ADMA molar ratio independently predicted the composite adverse clinical outcome and their mutual relationship was maintained upon adjustment for eGFR suggests that these prognostic effects were not entirely due to the association of abnormal levels of the biomarkers with impaired renal function (Fliser et al. 2005; Ravani et al. 2005, 2013; März et al. 2010; Røysland et al. 2012; Drechsler et al. 2013; Lewis et al. 2014).

Thus, high OPG and low hArg/ADMA ratio, albeit interrelated, appear to independently contribute to adverse clinical outcome. Admittedly, the underlying mechanisms connecting OPG with hArg and ADMA are still unresolved owing to their multiple, as yet not fully elucidated biological actions. The intriguing findings of our small preliminary study warrant further validation in large cohorts.

Acknowledgements This work was supported by Jagiellonian University Medical College (research Grant no. K/ZDS/006105 to A.S.). The funding source had no involvement in study design, in the collection, analysis and interpretation of data, in the writing of the report, and in the decision to submit the article for publication.

Compliance with ethical standards

Conflict of interest The authors declare that there no conflicts of interest.

Ethical approval The study was approved by the Bioethics Committee of the Jagiellonian University (ethical approval no. KBET/364/B/2012) in adherence to the Declaration of Helsinki.

Informed consent All participants provided written informed consent.

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